Glass Wool Fibers Expert Panel Report Part B

Glass Wool Fibers Expert Panel Report

Part B – Recommendation for Listing Status for Glass Wool Fibers and Scientific Justification for the Recommendation

The Report on Carcinogens (RoC) expert panel for glass wool fibers exposures met at the Sheraton Chapel Hill Hotel, Chapel Hill, North Carolina on June 9-10, 2009, to peer review the draft background document on glass wool fibers exposures and make a recommendation for listing status in the 12th Edition of the RoC.

Members of the expert panel are as follows:

Karl Kelsey, M.D., M.O.H., Chair
Department of Pathobiology and Laboratory Medicine
Brown University

Peter Lees, Ph.D., C.I.H.
Bloomberg School of Public Health
The Johns Hopkins University

Aaron Blair, Ph.D., M.P.H.
Occupational & Environmental Epidemiology Division of Cancer Epidemiology & Genetics
National Cancer Institute

Morton Lippmann, Ph.D.
Environmental Medicine
New York University School of Medicine

Michael Elwell, Ph.D., D.V.M.
Pathology Department
Covance Laboratories

Allan Smith, M.D., Ph.D.
School of Public Health
University of California, Berkeley

Kyle Steenland, Ph.D.
Rollins School of Public Health
Emory University

Andrij Holian, Ph.D.
Pharmaceutical Sciences
University of Montana

J. Michael Rigsbee, Ph.D.*
Department of Materials Science and Engineering
North Carolina State University

Marie-Claude Jaurand, Ph.D.
IFR105 – CEPH – IUH
INSERM U67 Paris

*Non-member, technical expert

The expert panel’s recommendation for listing status and the scientific justification for their recommendation follow.

Overall Evaluation

Following a discussion of the body of knowledge, the expert panel reviewed the RoC listing criteria and made its recommendation. The expert panel recommended by a vote of 8 yes/0 no that glass wool fibers, with the exception of special fibers of concern (characterized physically below), should not be classified either as known to be a human carcinogen or reasonably anticipated to be a human carcinogen.

The expert panel also recommended by a vote of 7 yes/0 no/1 abstention, based on sufficient evidence of carcinogenicity in well-conducted animal inhalation studies, that special-purpose glass fibers with the physical characteristics as follows — longer, thinner, less soluble fibers (for
example, \( \geq 15 \, \mu m \) length with a \( k_{\text{dlu}} \) of \( \leq 100 \, \text{ng/cm}^2/\text{h} \) — are reasonably anticipated to be a human carcinogen for the listing status in the RoC.

The major considerations discussed that led the panel to its recommendation include the observations of tumors in multiple species of animals (rats and hamsters). Both inhalation and intraperitoneal routes of exposure produced tumors, although inhalation was considered more relevant for humans.

Section 2. Human Exposure

While it is difficult to rigorously define differences between fiber categories in quantifiable scientific terms, there are two categories of glass wool – that used for thermal insulation and that used for special products – that may have different toxicologic effects. Differences between these categories are evident in terms of fiber diameters, fiber chemistry and resultant durability, production methods, and levels of exposure; although no bright line distinction exists, with the possible exception of the differences in their ultimate use which has historically formed the basis of this distinction.

There is well-documented historic and current exposure information for manufacturing and end-user populations; these populations have been estimated to number from a low of 15,000 to upwards of 200,000 exposed persons in the United States. The overwhelming preponderance of the exposure data is related to the glass wool product category while exposure data for special purpose glass, which is produced at a volume approximately 1% of the glass wool products, are far fewer and more dated. In broad terms, glass wool manufacturing populations have been exposed to fiber concentrations in the range of hundredths to tenths of fibers/cm\(^3\), generally as an 8-hour time weighted average; production of fibers that have been historically referred to as special purpose fibers have typically resulted in exposure levels 2 to 10 times higher. End user populations have been exposed in the range of tenths to single digit fibers/cm\(^3\), generally expressed as a task-length average. Downstream uses of specialty product fibers are mostly limited to fabrication operations incorporating them into products: however, there are no published data on these exposures. The potential for very low-level general population exposure also exists, generally on the order of \( 10^{-5} \) to \( 10^{-3} \) fibers/cm\(^3\).

Section 3. Human Cancer Studies

Several epidemiologic studies are available to evaluate cancer risks among workers with possible exposure to glass wool. Parts of the cohorts included persons exposed to specialty fibers but the workers were not specifically identified. These studies are all described in the background document. We relied most heavily on results from five cohort studies and one case-control study because they provided information on glass wool exposures (Table 1). Other studies may have included workers exposed to glass wool, but they did not provide direct evaluations of cancer risk among individuals specifically for that exposure. These studies varied in size, information on exposure, adjustments for possible confounders, and comparison populations, but they were all useful in the assessment of cancer and exposure to glass wool. The relevant studies provided considerable information on risk of lung cancer. Some information on other cancers was also available, but, except for mesothelioma, it was not sufficient to contribute to our evaluation and assessment.

Relative risks for lung cancer among workers potentially exposed to glass wool in these studies were 1.18 (95% CI, 1.04-1.34) among men in the U.S. cohort (Marsh et al. 2001), 1.02 (95% CI, 0.76-1.34) among women in the U.S. cohort (Stone et al., 2004), 1.27 (95% CI, 1.07-1.50) based on national mortality rates and 1.12 (95% CI, 0.95-1.31) based on local mortality rates in the European cohort (Boffetta et al. 1997), 1.28 (95% CI, 0.91-1.74) for cancer incidence in the
European cohort (Boffetta et al. 1999), 1.63 (95% CI, 1.18-2.21) for mortality and 1.63 (95% CI, 1.18-2.21) for incidence in the Canadian cohort (Shannon et al. 2005), and 0.74 (95% CI, 0.24-1.72) in a French cohort (Moulin et al. 1986). A case-control study of lung cancer in Russia reported a relative risk of 1.77 (95% CI, 0.57-5.51) among workers possibly exposed to glass wool (Baccarelli et al. 2006). A meta-analysis by Berrigan (2002) of respiratory cancer from 10 case-control studies and 10 cohort studies found an overall SMR of 1.23 (95% CI, 1.10-1.38) for glass wool. The meta-analysis included the cohort of Shannon et al. (2005), which appears to be an outlier, and included only national rates for the European cohort. Although Marsh et al. (2001) was able to perform some adjustment for possible confounding from tobacco use and asbestos exposure and Baccarelli et al. (2006) for tobacco use, other studies were unable to make such adjustments.

The small and rather consistent excesses of lung cancer observed in the studies above raise the possibility of a link between exposure to glass wool and development of lung cancer. Several limitations complicate interpretations for this assessment. Most studies could not adjust for possible confounders. The excesses of lung cancer observed in most of these studies are in the range that can easily be explained by confounding. These small excesses were not generally further supported by exposure-response trends, except for the study by Shannon et al. (2005), where the data showed increased risk with duration of exposure. Only the Marsh cohort provides quantitative estimates of exposure to glass wool (f/ml). We recognize that quantitative exposure assessment is difficult and prone to misclassification, which would tend to bias estimates of relative risks toward the null in cohort studies.

Mesothelioma is strongly linked to asbestos, and is extremely rare without this exposure. Unlike lung cancer, there is just one major established cause. The largest study in the U.S. showed that 88% of pleural mesothelioma in adult men was attributable to asbestos (Spirtas et al. 1994). The consequence of this is that for a subset of workers not known to have occupational exposure to asbestos, the "expected" numbers from the general population are gross overestimates, and the SMR for workers not known to be exposed to asbestos is underestimated. For this reason it is pertinent to identify if there are cases of mesothelioma with exposure to glass wool that were not known to have been exposed to asbestos. There are three studies identifying cases of mesothelioma not known to have been exposed to asbestos.

Marsh et al. (2001b) identified ten cases of mesothelioma with the word “mesothelioma” on their death certificates. Three had possible exposure to asbestos at the plants studied (one case 2.46 years, the second 0.38 years, and the third 2.18 fibers/cc months). The results of a questionnaire showed that five additional cases reported potential asbestos exposure at other job locations or within the glass wool industry. This leaves two cases with no known exposure to asbestos (Case 3 and Case 8). The mesothelioma diagnosis for Case 3 was questionable and there was no information concerning exposure to asbestos for the other case. In summary, there were no confirmed cases with a diagnosis of mesothelioma with work history indicating no potential exposure to asbestos.

Rodelsperger et al. (2001) studied 125 male cases of malignant mesothelioma in a case-control study in Germany. 114 cases had identified exposure to asbestos in their work histories. 2 cases and controls were exposed MMVF and 2 controls, giving an OR of 15.1 (95% CI = 1.05-218). In view of the difficulty in identifying occupational histories of exposure to asbestos, it remains possible that the 2 cases exposed to MMVF without known asbestos exposure actually had unidentified exposure to asbestos in the past. To place this in context, there were 53 cases with MMVF exposure that were found to have also had asbestos exposure. Engholm et al. (1987) studied approximately 135,000 construction workers in Sweden. Twenty-three cases of malignant mesothelioma were identified. Twelve of these cases were not identified as having had asbestos exposure, but there was no evidence that there was an increased risk of mesothelioma in the data presented for exposure to MMVF without asbestos exposure.
It should be noted that exposures in the glass wool cohorts were at least an order of magnitude lower than historical exposures for the asbestos cohorts that noted increases for lung cancer and mesothelioma (Armstrong et al. 1988, Levin et al. 1998, and Newhouse and Berry, 1985.)

Summary
There is insufficient evidence for the carcinogenicity of glass wool in humans. Despite small excesses of lung cancer in several studies, the less than complete adjustment for possible confounders and little evidence of exposure-response trends led us to conclude that these data do not provide credible support for a causal association. Careful evaluation of information on mesothelioma from these studies provides no evidence of confirmed cases with exposure to glass wool, but without exposure to asbestos.
Summary of findings from human cancer studies evaluating exposure to glass wool and lung or respiratory cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Results: lung cancer and glass wool exposure</th>
<th>Results lung cancer and glass wool exposure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted Risk estimate (95% CI); exposed cases or death</td>
<td>Adjusted risk estimate (95% CI); exposed cases or deaths</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality – SMR</td>
<td>Nested case-control study for lung and larynx in males only, RR adjusted for smoking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local rates</td>
<td></td>
<td>SMR for all SVF using national rates: 1.17 (95% CI = 1.09-1.25)</td>
</tr>
<tr>
<td></td>
<td>1.18 (1.04-1.34); 243</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marsh <em>et al.</em> 2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(U.S. – males and females)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant type</td>
<td>Filament 1.0 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GW + F</td>
<td>1.01 (0.69-1.47); 356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GW</td>
<td>1.06 (0.71-1.60); 183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No trends for duration of employment, time or time since first employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cumulative exposure (f/ml) 1.0 (0.93-1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stone <em>et al.</em> 2004</td>
<td>Internal analyses (RR): Multivariate model (model 3) includes formaldehyde exposure, cumulative exposure and duration of employment</td>
<td>Not adjusted for smoking</td>
<td></td>
</tr>
<tr>
<td>(U.S. – females)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality – SMR (local rates)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1.02 (0.76-1.34); 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>0.77 (0.72-0.82); 930</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Employment duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>1.0; 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>2.30 (1.21-4.38); 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19</td>
<td>0.80 (0.32-2.02); 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 +</td>
<td>0.63 (0.19-2.06); 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trend</td>
<td>$P = 0.02$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- SMR: Standardized Mortality Ratio
- CI: Confidence Interval
- RR: Relative Risk
- GW: Glass Wool
- F: Formaldehyde
- SVF: Silicon and Glass Fibre
- U.S.: United States
<table>
<thead>
<tr>
<th>Study</th>
<th>Results: lung cancer and glass wool exposure</th>
<th>Results lung cancer and glass wool exposure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Unadjusted Risk estimate (95% CI); exposed cases or death</strong></td>
<td><strong>Adjusted risk estimate (95% CI); exposed cases or deaths</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Boffetta et al. 1997 (European – males and females) | Mortality – SMR  
National rates  1.27 (1.07-1.50); 140  
Local rates  1.12 (0.95-1.31); 140 |  | Not adjusted for smoking |
|       | **Employment duration**  
Years | SMR  
1-4 | 1.11 (0.82-1.46); 50  
5-9 | 1.18 (0.80-1.68); 30  
10-19 | 1.68 (1.23-2.25); 45  
20 + | 1.17 (0.66-1.93); 15 |  | |
| Boffetta et al. 1999 (European – males and females) | Incidence – SIR  
National rates  1.28 (0.91-1.74); 40 | Internal analyses, RR adjusted for gender, age, country and technological phase  
**Employment duration + 15 year lag**  
Years | RR  
< 5 | 1.0 ref. 23  
5-10 | 0.8 (0.3-2.0); 8  
10-19 | 0.8 (0.3-2.4); 4  
20+ | 0.7 (0.08-5.3); 1 |  | Not adjusted for smoking |
| Moulin et al. 1986 (French – males) | Incidence – SIR  
Local rates  0.74 (0.24-1.72); 5 |  | No information on smoking |
| Shannon et al. 2005 (Canadian – males) | Mortality – SMR  
Local rates  1.63 (1.18-2.21); 42 |  | No information on smoking |
|       | **Employment duration**  
Years | SMR; deaths  
0 | 1.50; 13  
< 5 | 1.71; 4  
< 10 | 1.39; 8  
< 20 | 1.89; 17  
20+ | 1.89, P < 0.05  
20 + and > 40 time since first exposure |  | |
| Case-control studies |  |  |  |

*a*
<table>
<thead>
<tr>
<th>Study</th>
<th>Results: lung cancer and glass wool exposure Unadjusted Risk estimate (95% CI); exposed cases or death</th>
<th>Results lung cancer and glass wool exposure Adjusted risk estimate (95% CI); exposed cases or deaths</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Baccarelli et al. 2006 (Russian - males) | OR adjusted for smoking, age, residence and asbestos  
All (GW) 1.56 (0.49-5.02)  
OR adjusted for smoking, age, and residence  
All (GW) 1.77 (0.57-5.51); 10  
Average intensity  
MAC  
< 75% 0.83 (0.16-4.18)  
≥ 75% 3.61 (0.64-20.4)  
Cumulative exposure  
Scoreb  
< 5 1.79 (0.16-20.2)  
> 5 1.77 (0.49-6.36) | | |

Abbreviations: F=filaments, GW=glass wool, SVF=synthetic vitreous fibers, MAC= maximum allowable concentration, OR=odds ratio, RR=relative risk, SIR=standardized incidence ratio, SMR=standardized mortality ratio

* Only studies specific for GW are included; large case control studies by Pintos et al., Bruske-Holfeld et al., and Carel et al. are not included because they are based on all SVF, without discriminating for GW.

b Calculated as the product of average intensity score (ranging from 0.25 to 2.25) per total duration
Section 4. Animal Cancer Studies

Based on evaluation of long-term inhalation studies with glass wool fibers, the commercial use as designated in each study (insulation glass wool vs. special purpose fibers) was related to the carcinogenicity by this route of administration.

However, it is difficult to definitively separate these fibers into subcategories based on the criteria below.

1. Special Purpose Fibers vs. Insulation Glass Wool Fibers
According to the definition of special purpose fibers (SPF) provided in the Draft Background Document and in the Public comments, SPF contain specific elements such as Ba, Zn or Zr. This is not reported for several SPF fibers used in the animal experiments. SPF fibers are also supposedly more durable than a typical insulation glass wool. Moreover, there are some uncertainties. [For instance, Bayer B-1, B-2 are considered as SPF on page 6; classified as glass wool (GW) on page 196 (Table 5-1E). According to Table 1-4, on page 8, and Pott et al. 1991, they do not contain Ba, Zn or Zr. These elements are also not present in E-glass (E glass microfiber and JM104E), and JM753].

2. Physico-chemical subcategories
Criteria for separation of glass wool fiber into categories of insulation vs. special purpose fibers, especially concerning quantification of “durability” are not consistent. Physico-chemical properties related to carcinogenicity include surface properties, solubility and biopersistence. Surface properties were poorly investigated. Solubility, as assessed by Z-score does not discriminate carcinogenic and non-carcinogenic fibers. The significance of in vitro dissolution rate to the in vivo situation is difficult to extrapolate. Moreover, fibers prepared for animal experiments are treated to be respirable and may result in changes in their surface and physico-chemical properties.

3. Commercial subcategories
It is difficult to consider categories according to commercial labeled uses. While SPF and GW are commercialized for different purposes, there is a large diversity of chemical compositions, and those may vary with time, and diameters decrease as well. A commercial product may have different compositions. Subcategories according to uses may contain both glass wool and rock wool.

4. Mechanisms of carcinogenicity
Investigations of the mechanism of fiber carcinogenicity strongly suggest that physico-chemical properties are not sufficient to account for the carcinogenicity. Other variables including fiber dimensions, exposure dose and cumulative dose, contributed to the biopersistence.

Studies that are considered most informative for assessment of carcinogenic potential of insulation glass wool and special purpose glass wool fibers are those conducted by the inhalation route of exposure and are listed below. Studies conducted by other routes for insulation glass wool and special purpose fibers are also listed but results of those studies are of limited usefulness for predicting human risk for inhalation of fibers.

Glass wool fibers (insulation)
Inhalation studies
- There is evidence for carcinogenicity in rats based on an inhalation study by Mitchell et al. (1986) and Moorman et al. (1988) that showed an increased incidence of mononuclear-cell leukemia (MCL) in F344 rats exposed to Owens-Corning glass wool
fibers. However, there was no evidence of pulmonary or mesothelial carcinogenicity associated with inhaled fibrous glass.

- Hamsters exposed to MMVF10a (McConnell et al. 1999 and Hesterberg, et al. 1997) by the inhalation route showed no increases in lung tumors/mesothelioma.
- A number of earlier studies (Schepers and Delahant, 1955; Schepers, 1974; Gross et al. 1970) conducted by the inhalation route in several species did not result in an increase in lung tumors/mesothelioma. However, because of the design, they were of limited value for assessment of carcinogenic potential of glass wool insulation fibers.

Other routes
- An intraperitoneal injection study (Grimm, et al. 2002) in female Wistar rats resulted in increased incidence of mesothelioma with experimental biosoluble glass wool fibers B, P, and V.
- Intraperitoneal injection studies (Miller et al. 1999 and Roller et al. 1996, 1997) in Wistar rats resulted in increased incidence of mesothelioma with MMVF10 and MMVF11.
- Intrathoracic injection of Osborne Mendel rats administered insulation glass wool fibers (Glass 15 and Glass 12) resulted in one mesothelioma in each group (Stanton, et al. 1977,1981).

Glass wool fibers (special purpose)

Inhalation studies
- Sufficient evidence for carcinogenicity in animals is based on increase in lung tumors and mesothelioma in Wistar rats with inhalation exposure to 104E (Cullen et al. 2000); and mesothelial hyperplasia and mesothelioma in hamsters exposed to MMVF33 (McConnell et al. 1999 and Hesterberg, et al. 1997).
- There is evidence for carcinogenicity in rats, based on an inhalation study by Mitchell et al. (1986) and Moorman et al. (1988), which showed an increased incidence of MCL in F344 rats exposed to Tempstran 100/475. However, there were no increases in lung tumors/mesothelioma in that study.

Other routes
<table>
<thead>
<tr>
<th>Fiber type/source</th>
<th>Exposure route</th>
<th>Species</th>
<th>Inhalation</th>
<th>Intraperitoneal</th>
<th>Intratracheal</th>
<th>Intrathoracic</th>
<th>Intrapleural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulation wool</td>
<td></td>
<td>Rat (not specified)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wistar</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sprague-Dawley</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osborne-Mendel</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F344</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syrian golden hamster</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guinea pigs</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BALB/c mice</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rabbits</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SPF</td>
<td></td>
<td>Wistar</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>SPF 475 glass</td>
<td></td>
<td>Sprague-Dawley</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>SPF 753 glass</td>
<td></td>
<td>Osborne-Mendel</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SPF 475 glass</td>
<td></td>
<td>F344</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SPF 475 glass</td>
<td></td>
<td>Syrian golden hamster</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>±</td>
</tr>
<tr>
<td>SPF E glass</td>
<td></td>
<td>Wistar</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SPF 753 glass</td>
<td></td>
<td>Experimental fibers</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

– = negative studies; + = positive studies (unless otherwise noted, considered as a treatment-related effect for lung tumors, mesothelioma/sarcoma by study authors); ± = both positive and negative studies.

*These studies reported an increase in mononuclear cell leukemia, but no respiratory or mesothelial tumors. In one study (insulation glass wool), there was a trend for an increase in total lung tumors (P=0.047).

b The positive study reported mesothelial hyperplasia and one mesothelioma.
Comments on Table:

**Glass wool fibers (insulation)**

*Inhalation studies*
- F344 rats: Increased incidence of MCL with exposure to Owens-Corning glass wool fibers in males and females from two dose groups of different diameter/fiber length.
- F344 rats: No neoplastic effects with exposure to MMVF11 and MMVF10 fibers.
- Syrian golden hamster: No neoplastic effect with exposure to MMVF10a fibers

*Other routes*
- Wistar rats: A positive carcinogenic response in rats administered insulation glass fibers (B glass) by intraperitoneal injection.
- Osborne-Mendel: A weak positive response in rats administered insulation glass wools by intrathoracic injection.

**Glass wool fibers (special purpose)**

*Inhalation studies*
- Wistar rats: increased incidence of lung tumors and mesothelioma with exposure to 104E.
- Hamster: Increased incidence of mesothelial hyperplasia and mesothelioma with exposure to MMVF33.
- F344 rats: Increased incidence of MCL with exposure to Tempstran 100/475 (two dose groups of different fiber length but no apparent difference in incidence between groups)

*Other routes*
- Rats (F344, Sprague-Dawley, Osborne Mendel) and hamsters had increased incidence of mesothelioma when administered special purpose glass fibers (475 glass, E glass, 753 glass, experimental fibers) by the intraperitoneal, intratracheal or intrapleural routes.

**Other issues to consider:**

Study design (route of exposure) and the relevance to assessment of a carcinogenic effect with exposure to glass wool fibers (ability to establish/assess an MTD).

Specific criteria for separation of glass wool fibers into categories of insulation glass wool vs. special purpose fibers are not always consistent, especially concerning quantification of “durability”.

Size and amount of fibers deposited in the lung should be taken into consideration in interpretation of the data, with the same attention as “durability”.

Recommend limited evidence of carcinogenicity in animals for insulation glass wool fibers based on an increase in MCL in one strain of rats (F344) from a single study. In addition, there was a positive carcinogenic response in one strain (Wistar) of rats administered insulation glass wool by intraperitoneal injection and a weak positive response in one strain (Osborne-Mendel) of rats by intrathoracic injection. These additional studies were considered to represent non-physiological routes of exposure but provided informative results as screening tests for hazard assessment. Low tumor yield with insulation glass wool by the intracavitary routes was generally not associated with an increase in lung tumors if tested by the inhalation route.
Recommend sufficient evidence for carcinogenicity in animals administered special purpose glass fibers based on positive studies in rats and hamsters by the inhalation route. In addition, a carcinogenic response occurred in several strains of rats injected with special purpose fibers by the intraperitoneal, intrapleural and intratracheal routes. Positive responses also occurred in rats injected by the intrathoracic route and hamsters injected by the intratracheal route, but were considered to have limitations related to route of administration.

Section 5. Other Relevant Data

1. Glass fiber characteristics

Glass fibers may be physically (not by use) divided broadly into: 1) glass wools with relatively large diameters, high biosolubilities, and low biopersistence; and 2) special purpose fibers that are generally characterized by relatively smaller diameters, lower biosolubilities, and higher biopersistence.

The chemical compositions of these fibers (i.e., various metal oxides dissolved within the glass) contribute to the variability in biopersistence and biosolubility of the fibers. Relatively long fibers (approximately >15 μm) are important because macrophages have difficulty clearing fibers that are longer than the macrophage diameter and may result in death of the macrophage and release of inflammatory mediators. In order to provide some guidance to distinguish these two types of fibers, our review of the literature suggests that fibers with a \( K_{\text{dis}} \) of \( \geq 100 \text{ ng/cm}^2/\text{h} \) and lengths <15 μm are unlikely to be of particular concern.

2. Fiber deposition and retention

The deposition of fibers is determined primarily by their aerodynamic diameters with enhancement of deposition of fibers with lengths greater than 10 μm due to interception at the airway wall. Clearance and retention of deposited fibers are influenced by fiber length as discussed above. Retention is also influenced by fiber dissolution. Low biopersistent fibers would result in a net lower level of total accumulation in the lung, even with continued exposure, while more biopersistent fibers would result in continual accumulation in the lung with continued exposure. The ultimate steady-state number of fibers would increase as biopersistence increases.

3. Genotoxicity

The data indicate that fibers have the potential to cause genetic damage \textit{in vitro}. However, extrapolation from these data to carcinogenicity is problematic.

4. Mechanistic data

Although the available data are not sufficient to define the exact mechanism(s), the data suggest that an underlying chronic inflammatory response is required. Experimental data indicate that long, biodurable fibers are likely to be accompanied by a chronic inflammatory response. There are no data to suggest that the proposed mechanisms are not relevant to humans.

[Redacted]

Report Approved: July 21, 2004

Karl Kelsey, M.D., M.O.H., Chair

Date
References


